PSA Fluktuationen nach permanenter JOD-125 Seed Brachytherapie beim frühen Prostatakarzinom und die Bedeutung der Bild-geführten Brachytherapie in der kurativen Behandlung des Prostata- und des Zervixkarzinomes

Zwahlen, D R

MEDIZINISCHE FAKULTÄT ZÜRICH

UNIVERSITÄTSSPITAL ZÜRICH

KLINIK UND POLIKLINIK FÜR RADIOONKOLOGIE

DIREKTOR: PROF. DR. MED. U.M. LÜTOLF

PSA FLUKTUATIONEN NACH PERMANENTER JOD-125 SEED BRACHYTHERAPIE BEIM FRÜHEN PROSTATAKARZINOM

UND

DIE BEDEUTUNG DER BILD-GEFÜHRTEN BRACHYTHERAPIE IN DER KURATIVEN BEHANDLUNG DES PROSTATA- UND DES ZERVIXKARZINOMES

HABILITATIONSSCHRIFT

ZUR ERLANGUNG DER VENIA LEGENDI DER MEDIZINISCHEN FAKULTÄT

DER UNIVERSITÄT ZÜRICH

VORGELEGT VON

DANIEL RUDOLF ZWAHLEN

VON WAHLERN BE

APRIL 2010

TEIL 1

PSA FLUKTUATIONEN NACH PERMANENTER JOD-125 SEED BRACHYTHERAPIE BEIM FRÜHEN PROSTATAKARZINOM

1 ORIGINALARBEIT

TEIL 2

DIE BEDEUTUNG DER BILD-GEFÜHRTEN BRACHYTHERAPIE IN DER KURATIVEN BEHANDLUNG DES PROSTATA- UND DES ZERVIXKARZINOMES

2 ORIGINALARBEITEN MIT KOMMENTAREN

HABILITATIONSSCHRIFT VON DANIEL RUDOLF ZWAHLEN

ALS HABILITATIONSSCHRIFT VORGELEGTE PUBLIKATIONEN UND KOMMENTARE

TEIL 1:PSA FLUKTUATIONEN NACH PERMANENTER JOD-125 SEED BRACHYTHERAPIE BEIM FRÜHEN PROSTATAKARZINOM

Zwahlen DR, Smith R, Andrianopoulos N, Matheson B, Royce P, Millar JL (2010) Prostate-specific antigen bounce after permanent iodine-125 prostate brachytherapy – an Australian analysis.
Int J Radiat Oncol Biol Phys. April 10 [Epub ahead of print]

Teil 2: DIE BEDEUTUNG DER BILD-GEFÜHRTEN BRACHYTHERAPIE IN DER KURATIVEN BEHANDLUNG DES PROSTATA- UND DES ZERVIXKARZINOMES

Zwahlen DR, Andrianopoulos N, Matheson B, Duchesne GM, Millar JL (2010) High-dose-rate brachytherapy in combination with conformal external beam radiotherapy in the treatment of prostate cancer. Brachytherapy. 9: 27-35

Zwahlen D, Jezioranski J, Chan P, Haider MA, Cho YB, Yeung I, Levin W, Manchul L, Fyles A, Milosevic M (2009) Magnetic resonance imaging-guided intracavitary brachytherapy for cancer of the cervix.
Int J Radiat Oncol Biol Phys. 74: 1157-1164

Table of Contents

Background 2

Is there a role for image-guided high-dose rate (HDR) brachytherapy to improve the cure rate for patients diagnosed with prostate cancer? 5

1. Introduction 5
2. Our results 6
   - 2.1 Methods 6
   - 2.2 Results 7
   - 2.3 Summary 7
   - 2.4 Conclusion 8

Can MRI-guided intracavitary brachytherapy improve tumour dosimetry and reduce dose to critical normal structures? 10

1. Introduction 10
2. Our results 11
   - 2.1 Methods 11
   - 2.2 Results 12
   - 2.3 Summary 12
   - 2.4 Conclusion 13

Outlook 15

References 16

Background

An important underlying principle in radiation oncology is to enhance tumour control by delivering the highest dose to the tumour whilst minimizing toxicity to the surrounding normal tissues. This optimisation of the therapeutic ratio remains an ongoing challenge for radiation oncologists in their search for the optimal treatment modality. However, major technological advances have improved the delivery of external beam radiation therapy (EBRT). For example, the integration of computed tomography (CT) imaging and computer-assisted dose calculation algorithms have resulted in three-dimensional (3D) image-based treatment planning and delivery. Intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) represent a further important advancement, as these provide the opportunity to sculpt the dose distribution to almost any complex-shaped target volume, whilst sparing adjacent normal structures (1).

Although EBRT has experienced dramatic technological innovations, similar developments in brachytherapy have not been attained. Historically, brachytherapy was among the first established and successful techniques for conformal cancer treatment as it delivers a high tumour dose with a rapid dose fall off, leading to sparing of normal tissues. For these reasons, it has remained a fundamental treatment component in radiation oncology since the early twentieth century. Traditionally, brachytherapy planning and treatment has been based on orthogonal radiography. Although dose distribution was calculated in three dimensions it could not be viewed in 3D relative to the patient anatomy. In recent years, brachytherapy practice has adopted the exciting technological concepts of 3D image-guided EBRT. Development in cross-sectional imaging with CT, magnetic resonance imaging (MRI) and real-time

ultrasound-guided techniques, coupled with sophisticated dosimetric planning systems, have enabled the accurate and reliable delivery of highly conformal radiotherapy using brachytherapy (2).

There is strong interest to integrate 3D image-based brachytherapy into the management of several cancer sites, including prostate cancer and cervix cancer. The use of brachytherapy for prostate cancer allows the delivery of hypofractionated radiation therapy, thereby conferring a therapeutic radiobiological advantage (3). High-dose rate (HDR) afterloading systems allow greater flexibility of source loading patterns and dose delivery that makes it an attractive technology for dose escalation. Low-dose rate (LDR) permanent seed brachytherapy for early stage prostate cancer is another technology that has become increasingly popular due to the ability to place seeds accurately under real-time transrectal ultrasound guidance (4, 5). Such techniques have advantages for both the patient and treatment centre due to the significant decrease in treatment time, improving patient convenience and treatment accessibility, respectively (6). For cervix cancer, image-guided brachytherapy combines greater accuracy in tumour volume definition with reduced dose to the adjacent organs at risk.

However, the implementation of new and innovative technologies relies upon careful and thorough analysis of both the effectiveness and safety of the treatment. Whilst randomised controlled trials are the most rigorous form of analysis, the performance of such trials is not always possible for both practical and scientific reasons. Additionally, whilst multi-institutional collaboration is desirable, this may not be achievable due to the conflicting areas of interest and expertise in radiation oncology departments. It is therefore imperative that careful evaluation of innovative technologies, such as those employed in modern brachytherapy, are undertaken by those centres wishing to

implement or enhance their brachytherapy program. Analysing the benefits and potential detriments of image-guided brachytherapy is fundamental to understanding its role in future radiation oncology paradigms, as well as the potential impact on the workload of a brachytherapy program.

Here we summarize our work on the role of image-guided brachytherapy in prostate and cervix cancer, with a view to providing recommendations for the implementation of a prostate brachytherapy program and to further optimise the delivery of safe and effective brachytherapy for cervix cancer.

Is there a role for image-guided high-dose rate (HDR) brachytherapy to improve the cure rate for patients diagnosed with prostate cancer?

1. Introduction

The biological advantage of HDR brachytherapy relates to the ability to deliver higher radiation dose per fraction safely and with high conformation to the prostate gland. There is evidence that prostate cancer cells respond favourably to radiation delivered at large dose per fraction described by a survival curve with a low α/β ratio. The actual figure remains unknown, but most investigators suggest it is well below five and possibly as low as two or three, with extreme estimates as low as 1.5 Gy (3, 7-10). The significance of this is that dose escalation via hypofractionation is biologically advantageous due to the comparatively lower sensitivity to fractionation changes of surrounding critical organs, such as bladder and rectum (α/β ratio = 3-5 Gy). Thus, hypofractionation most likely increases tumour cell killing effect.

HDR brachytherapy is often used as a boost in conjunction with external beam radiation therapy. In general, patients treated with HDR brachytherapy present with unfavourable prognostic factors, such as palpable tumour or extracapsular disease, higher Gleason score and pre-treatment PSA greater than 10 ng/ml (11). Results from two randomized controlled trials (12, 13) and single institutional reports of HDR brachytherapy in combination with EBRT confirm HDR brachytherapy as an alternative technique for dose-escalation, with tumour control rates similar to those obtained with EBRT alone. Estimated 5- and 8-year biochemical free survival ranges from 65% to over 90%, dependent on the number of risk factors present (14-17)

2. Our results

Dose escalation with 3D conformal external beam radiation therapy (3DCRT) or IMRT improves outcome with acceptable toxicity profiles (18, 19). HDR brachytherapy in combination with 3DCRT is an alternative method with the ability to deliver a highly conformal radiation treatment with a favorable toxicity profile. The purpose of our study was to report the outcomes of 196 men treated with HDR brachytherapy for dose escalation in combination with 3DCRT, and compare them with 387 men treated contemporaneously with 3DCRT alone (20).

2.1 Methods

From 1998 to 2003, 587 patients were treated at The William Buckland Radiotherapy Centre (Monash University, Melbourne, Australia) for clinically localized prostate cancer. Patients received either 3DCRT (median 46 Gy) with a single HDR brachytherapy implant (196 patients) delivering a fractionated dose of 18 Gy (combined group), or 3DCRT (median 70 Gy, 387 patients, “3DCRT alone”). There were 41.9% intermediate-risk and 42.6% with high-risk disease. In all, 441 patients (75.1%) received neoadjuvant and 116 patients (19.8%) adjuvant androgen deprivation therapy (ADT). The American Society of Therapeutic Radiology and Oncology (ASTRO) Phoenix definition for biochemical failure was used.

2.2 Results

Median follow-up was 5.5 years. The 5-year and 7-year biochemical control (BC) rates were 82.5% and 80.3% for the combined group and 81.3% and 71% for 3DCRT alone; for overall survival they were 91.9% and 89.5% vs. 88.7% and 86.2% (n.s.); whilst cause-specific survival was 96.9% and 96.1% vs. 97.6% and 96.2% (n.s.), respectively. Cox proportional hazard regression analysis for BC revealed that low Gleason grade, HDR brachytherapy combined with 3DCRT and adjuvant ADT were significant in predicting BC. RTOG grade 3 late urinary and rectal morbidity rates were 7.1% and 0% for HDR brachytherapy in combination with 3DCRT, respectively. No grade ≥ 4 reactions were detected.

2.3 Summary

Similar to other reports including randomized clinical trials, we demonstrated that 3DCRT combined with HDR prostate brachytherapy resulted in excellent long-term biochemical control, overall survival and cause-specific survival (12-14, 16, 17, 21-24). On multivariable analysis, combined treatment was associated with a statistically significant improved biochemical control of 36% ($p = 0.047$) when compared to 3DCRT alone, adjusting for adverse risk factors in the combined group. No RTOG Grade 4 urinary or rectal morbidities were observed.

2.4 Conclusion

Image-guided HDR brachytherapy has gained an important role in the management of localized prostate cancer. There is a strong dose-response relationship in prostate cancer and HDR brachytherapy provides an efficient method to achieve dose escalation that is needed for improved cancer control with low toxicity.

There are a number of reasons to justify the establisment of a HDR prostate brachytherapy program. Overall treatment time is shortened using hypofractionation, which is more convenient for patients, and the HDR brachytherapy implant circumvents organ motion thereby avoiding the need for wide safety margins during treatment application. In contrast, delivering dose escalation with conventional EBRT fractionation requires a prolonged treatment time of 8 to 9 weeks using correction for daily organ motion with image guidance, resulting in more costly and less time efficient treatment for the patient and the radiation oncology department (25). The treatment optimization process with HDR brachytherapy allows varying dose distributions across the target and selective dosing of the peripheral zone or boosting of a dominant intraprostatic lesion (26). Additionally, HDR prostate brachytherapy allows for greater sparing of rectum and bladder than is achievable with EBRT alone (27, 28). The main disadvantages of HDR brachytherapy include the relative invasiveness of the procedure and the specialised skill set required (29).

With a better understanding of this technique combined with the current trend to use hypofractionation in the curative treatment of prostate cancer, further improvements in cancer control may be possible. Clinical studies comparing image-guided HDR brachytherapy using different fractionation schemes in combination with EBRT with dose-escalated EBRT alone are in progress (29). Such studies will ensure that all relevant factors, including economic perspective, are taken into account when deciding

upon the optimal treatment strategy to improve cure rates for patients with prostate cancer in the future.

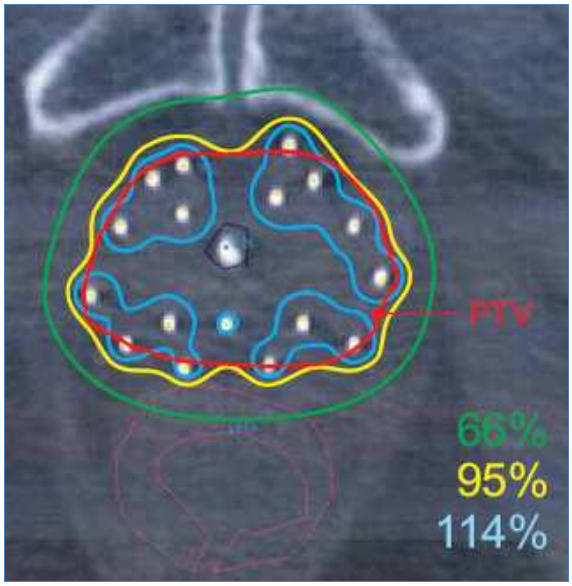

Figure 4. CT-scan image before brachytherapy treatment delivery with transperineally inserted temporary sealed-tip hollow catheters into the prostate gland. Red indicates planning target volume (PTV) and prostate; light blue, 114% isodose line; yellow and green, 95% and 66% isodose lines, respectively. Urethra=dark blue, Rectum=purple

Picture: Courtesy of A/Prof Jeremy L Millar
The William Buckland Radiotherapy Centre
Melbourne, Australia

Can MRI-guided intracavitary brachytherapy improve tumour dosimetry and reduce dose to critical normal structures?

1. Introduction

With evolving clinical experience with image-guidance in radiation oncology, a number of institutions have implemented MRI-based brachytherapy treatment for the curative management of cervical cancer. Tumour extension is imaged at the time of diagnosis and at the time of brachytherapy in order to individualize target volumes, thereby taking into account the tumour response over time. At the same time, the dose to organs at risk is adapted in relation to the applicator in 3D. Thus, with the assistance of image-guidance, dose escalation to the target volumes is achieved to ensure improved local control (30, 31).

The use of MRI in the staging process of cervical cancer, complementary to the clinical International Federation of Gynaecology and Obstetrics (FIGO) criteria, is well established (32, 33) and has become the investigation of choice to assess tumour extension prior to any treatment decision. For brachytherapy, the important role of MRI is afforded by the superior contrast resolution and image quality of soft tissues in the pelvis compared with ultrasound or CT (34, 35). Importantly, MRI enables the visualisation of cervical tumour size and volume, distinction of tumour from normal uterus or cervix and extension of disease into parametrial or vaginal tissues (36). T1- and T2-weighted axial, coronal and sagittal MRI scans with contrast using a pelvis surface coil are the preferred sequences (37). In particular, T2-weighted images of the cervical tumour display an increased signal intensity compared to normal cervical stroma, whereas paracervical soft tissues show high signal intensity on T1- and T2-

weighted images (38). It has been demonstrated that the use of MRI compared to CT provides information for more precise topographic definition and delineation of tumour extension and equal precision for organs at risk in relation to the applicator, and is thus integral to brachytherapy planning (35, 39, 40).

2. Our results

The purpose of our study was to report on the benefits of 20 patients whose treatment has been optimized with 3D MRI image-guided intracavitary brachytherapy, and compare it to conventional two-dimensional (2D) brachytherapy planning (41).

2.1 Methods

A total of 20 patients with International Federation of Gynaecology and Obstetrics (FIGO) stage IB-IV cervix cancer had an MRI-compatible intrauterine BT applicator inserted after external beam radiotherapy (EBRT). MRI scans were acquired, and the gross tumour volume at diagnosis (GTV_D) and at BT (GTV_B), the high (HR) and intermediate risk (IR) clinical target volume (CTV), and the rectal, sigmoid and bladder walls were delineated according to the recommendations of the Groupe Européen de Curiethérapie – European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) Working Group (Figure 1) (42, 43). Pulsed-dose-rate BT was planned and delivered in a conventional manner. Optimized MRI-based plans were developed and compared to the conventional plans.

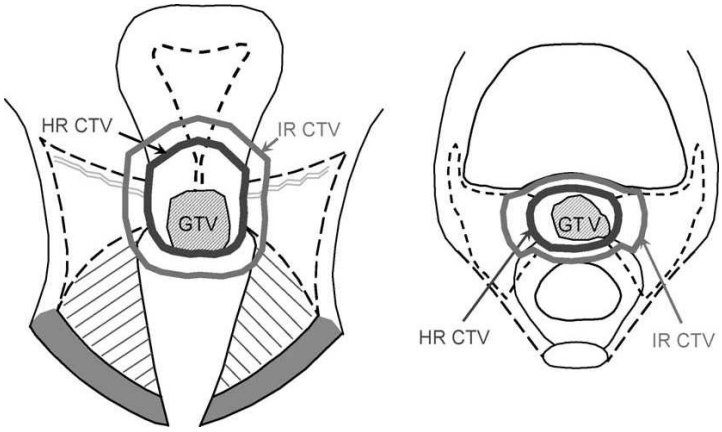

Figure 1. Schematic diagram for cervix cancer, limited disease, with gross tumour volume (GTV), intermediate risk (IR) clinical target volume (CTV) and high risk (HR) CTV for definitive treatment; coronal and transversal view) (42, 43)

2.2 Results

The HR CTV and intermediate-risk CTV were adequately treated (the percentage of volume treated to ≥ 100% of the intended dose was > 95%) in 70% and 85% of patients with the conventional plans, respectively, and in 75% and 95% of the patients with the optimized plans, respectively. The minimal doses to the contiguous 2 cm^3 of the rectal, sigmoid and bladder wall were 16±6.2, 25±8.7 and 31±9.2 Gy, respectively. With MRI-guided BT optimization, it was possible to maintain coverage of the HR CTV and reduce the dose to normal tissues, especially in patients with small tumours at the time of BT ($p < 0.05$). In these patients, the HR percentage of volume treated to ≥ 100% of the intended dose approached 100% in all cases, and the minimal dose to the contiguous 2cm^3 of the rectum, sigmoid and bladder was 12-32% less than with conventional BT planning.

2.3 Summary

The significant reduction in the contiguous 2 cm^3 doses to rectum, sigmoid and bladder has the potential to substantially reduce morbidity, given that current treatment

approaches have escalated the dose to the point at which even small incremental changes can translate into large clinical effects (44). This is in contrast to patients with large residual tumours at the time of brachytherapy, for whom the objective of adequate target coverage might preclude significant sparing of organs at risk. Among our patients with large target volumes, no difference was found between the optimized and conventional sigmoid and bladder $D2cm^3$ values, and the optimized rectal $D2cm^3$ increased by 14%. As a consequence, patients with large residual tumour bulk after external beam radiation therapy are probably not optimally treated with intracavitary brachytherapy alone, and instead should be considered for either a combination of intracavitary and interstitial brachytherapy (31, 45) or an IMRT boost (46). Our group will evaluate this as patient follow up matures (47).

2.4 Conclusion

Brachytherapy is integral to the successful management of cervix cancer, and in particular, intracavitary treatment permits delivery of a high dose of radiation to the cervix and paracervical tissues while minimizing dose to the bladder and bowel. Advances in imaging and computer dosimetry have been implemented into gynaecologic brachytherapy (2). However, it is necessary to evaluate the clinical benefit and associated costs of this complex system of MRI-based 3D treatment planning and performance of gynaecologic brachytherapy, as presented by our group. These include access to an MRI scanning device, MRI compatible applicators, digital network with integration of a 3D imaging device and interface for data transfer, 3D treatment planning system, trained personnel (physicians, physicists, radiotherapy technicians, nurses) and a multidisciplinary team approach. Potter *et al*. estimated the

additional costs necessary for setting up a MRI-based gynaecologic brachytherapy to be 10-15% higher of the normal costs of conventional brachytherapy (44). In addition, several patient and technical factors remain to be addressed in relation to the integration of MRI-based brachytherapy into routine clinical practice. This includes the identification of the appropriate patient population, the challenges of real-time contouring and plan optimization, the refinement of normal tissue constraints, improved understanding of the biology underlying tumour regression in relation to target dose optimization, and geometric and dosimetric stability during applicator insertion. This should be performed in a multicentre setting, using a combined intracavitary and interstitial approach, as well as state of the art external beam radiation therapy. The large, international, multicenter European Study on MRI-guided brachytherapy in locally advanced cervical cancer (EMBRACE) (www.clinicaltrials.org, www.embracestudy.dk) will be instrumental in addressing these issues and advancing the use of brachytherapy in this disease (31). If this proves to be feasible, there is large potential to increase disease control and overall survival in patients with locally advanced cervical cancer in the near future.

Outlook

Modern brachytherapy has made significant progress and obstacles towards image-guided brachytherapy for prostate and cervix cancer have been overcome. Numerous reports including our results showed that with the support of image guidance high-dose conformal radiotherapy is being delivered through modern brachytherapy techniques (2). Given their ability to deliver highly conformal dose distributions, it is not surprising that modern brachytherapy has been suggested as an alternative for sophisticated EBRT techniques including IMRT. Thus, radiation oncologists are facing the challenge that there are many advanced radiotherapy solutions from whitch to make a choice. The number of options is even larger when considering all the potentially beneficial combinations of radiotherapy modialities or dose fractionation schemes in addition to various chemotherapy and surgery solutions. Recently, the use of robotic-guided brachytherapy at gynaecological and genitourinary sites has been presented (48, 49). This may set another trend the way brachytherapy will be delivered. In todays health care environment the treatment decision is not only driven by forces improving treatment succes, but also by economy, patient safety, preference and convenience. As one in three Europeans will be diagnosed with cancer at some time in their lives and the number affected will increase as people live longer (50), these questions of how to choose the appropriate treatment are becoming very important. However, improving therapeutic outcome means selecting the right combinaiton of therapies and to have these available requries timely investment in working relationships, skills and technologies. In this complex environment, careful evaluation of new technologies, such as those employed in modern brachytherapy, remains key to practice best paitent care in the 21st century.

References

1. Galvin JM, De Neve W. Intensity modulating and other radiation therapy devices for dose painting. *J Clin Oncol* 2007;25:924-930.
2. Hoskin PJ, Bownes P. Innovative technologies in radiation therapy: brachytherapy. *Semin Radiat Oncol* 2006;16:209-217.
3. Duchesne GM, Peters LJ. What is the alpha/beta ratio for prostate cancer? Rationale for hypofractionated high-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 1999;44:747-748.
4. Sahgal A, Roach M, 3rd. Permanent prostate seed brachytherapy: a current perspective on the evolution of the technique and its application. *Nat Clin Pract Urol* 2007;4:658-670.
5. Zwahlen DR, Smith R, Andrianopoulos N*, et al.* Prostate-Specific Antigen Bounce After Permanent Iodine-125 Prostate Brachytherapy-An Australian Analysis. *Int J Radiat Oncol Biol Phys* 2010.
6. Miles EF, Lee WR. Hypofractionation for prostate cancer: a critical review. *Semin Radiat Oncol* 2008;18:41-47.
7. Bentzen SM, Ritter MA. The alpha/beta ratio for prostate cancer: what is it, really? *Radiother Oncol* 2005;76:1-3.
8. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1999;43:1095-1101.
9. Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumors really low? *Int J Radiat Oncol Biol Phys* 2001;50:1021-1031.
10. Williams SG, Taylor JM, Liu N*, et al.* Use of individual fraction size data from 3756 patients to directly determine the alpha/beta ratio of prostate cancer. *Int J Radiat Oncol Biol Phys* 2007;68:24-33.
11. NCCN. Clinical Practice Guidelines in Oncolgy. Prostate Cancer. V.I.2008 ed; 2008.
12. Hoskin PJ, Motohashi K, Bownes P*, et al.* High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. *Radiother Oncol* 2007;84:114-120.
13. Sathya JR, Davis IR, Julian JA*, et al.* Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol* 2005;23:1192-1199.
14. Duchesne GM, Williams SG, Das R*, et al.* Patterns of toxicity following high-dose-rate brachytherapy boost for prostate cancer: mature prospective phase I/II study results. *Radiother Oncol* 2007;84:128-134.
15. Galalae RM, Martinez A, Mate T*, et al.* Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;58:1048-1055.
16. Kalkner KM, Wahlgren T, Ryberg M*, et al.* Clinical outcome in patients with prostate cancer treated with external beam radiotherapy and high dose-rate iridium 192 brachytherapy boost: a 6-year follow-up. *Acta Oncol* 2007;46:909-917.

17. Phan TP, Syed AM, Puthawala A*, et al.* High dose rate brachytherapy as a boost for the treatment of localized prostate cancer. *J Urol* 2007;177:123-127; discussion 127.
18. Dearnaley DP, Sydes MR, Graham JD*, et al.* Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007;8:475-487.
19. Zelefsky MJ, Chan H, Hunt M*, et al.* Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. *J Urol* 2006;176:1415-1419.
20. Zwahlen DR, Andrianopoulos N, Matheson B*, et al.* High-dose-rate brachytherapy in combination with conformal external beam radiotherapy in the treatment of prostate cancer. *Brachytherapy* 2009.
21. Demanes DJ, Rodriguez RR, Schour L*, et al.* High-dose-rate intensity-modulated brachytherapy with external beam radiotherapy for prostate cancer: California endocurietherapy's 10-year results. *Int J Radiat Oncol Biol Phys* 2005;61:1306-1316.
22. Pellizzon AC, Salvajoli J, Novaes P*, et al.* Updated results of high-dose rate brachytherapy and external beam radiotherapy for locally and locally advanced prostate cancer using the RTOG-ASTRO Phoenix definition. *Int Braz J Urol* 2008;34:293-301.
23. Sato M, Mori T, Shirai S*, et al.* High-dose-rate brachytherapy of a single implant with two fractions combined with external beam radiotherapy for hormone-naive prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;72:1002-1009.
24. Vargas C, Martinez A, Galalae R*, et al.* High-dose radiation employing external beam radiotherapy and high-dose rate brachytherapy with and without neoadjuvant androgen deprivation for prostate cancer patients with intermediate- and high-risk features. *Prostate Cancer Prostatic Dis* 2006;9:245-253.
25. Nguyen PL, Zietman AL. High-dose external beam radiation for localized prostate cancer: current status and future challenges. *Cancer J* 2007;13:295-301.
26. Ares C, Popowski Y, Pampallona S*, et al.* Hypofractionated Boost with High-Dose-Rate Brachytherapy and Open Magnetic Resonance Imaging-Guided Implants for Locally Aggressive Prostate Cancer: A Sequential Dose-Escalation Pilot Study. *Int J Radiat Oncol Biol Phys* 2009.
27. Hsu IC, Pickett B, Shinohara K*, et al.* Normal tissue dosimetric comparison between HDR prostate implant boost and conformal external beam radiotherapy boost: potential for dose escalation. *Int J Radiat Oncol Biol Phys* 2000;46:851-858.
28. Pieters BR, van de Kamer JB, van Herten YR*, et al.* Comparison of biologically equivalent dose-volume parameters for the treatment of prostate cancer with concomitant boost IMRT versus IMRT combined with brachytherapy. *Radiother Oncol* 2008.
29. Morton GC. The emerging role of high-dose-rate brachytherapy for prostate cancer. *Clin Oncol (R Coll Radiol)* 2005;17:219-227.
30. Dimopoulos JC, Lang S, Kirisits C*, et al.* Dose-Volume Histogram Parameters and Local Tumor Control in Magnetic Resonance Image-Guided Cervical Cancer Brachytherapy. *Int J Radiat Oncol Biol Phys* 2009.

31. Potter R, Kirisits C, Fidarova EF*, et al.* Present status and future of high-precision image guided adaptive brachytherapy for cervix carcinoma. *Acta Oncol* 2008;47:1325-1336.
32. Hricak H, Lacey CG, Sandles LG*, et al.* Invasive cervical carcinoma: comparison of MR imaging and surgical findings. *Radiology* 1988;166:623-631.
33. Togashi K, Nishimura K, Sagoh T*, et al.* Carcinoma of the cervix: staging with MR imaging. *Radiology* 1989;171:245-251.
34. Ho CM, Chien TY, Jeng CM*, et al.* Staging of cervical cancer: comparison between magnetic resonance imaging, computed tomography and pelvic examination under anesthesia. *J Formos Med Assoc* 1992;91:982-990.
35. Viswanathan AN, Dimopoulos J, Kirisits C*, et al.* Computed tomography versus magnetic resonance imaging-based contouring in cervical cancer brachytherapy: results of a prospective trial and preliminary guidelines for standardized contours. *Int J Radiat Oncol Biol Phys* 2007;68:491-498.
36. Hricak H, Yu KK. Radiology in invasive cervical cancer. *AJR Am J Roentgenol* 1996;167:1101-1108.
37. Nag S, Cardenes H, Chang S*, et al.* Proposed guidelines for image-based intracavitary brachytherapy for cervical carcinoma: report from Image-Guided Brachytherapy Working Group. *Int J Radiat Oncol Biol Phys* 2004;60:1160-1172.
38. Schoeppel SL, Ellis JH, LaVigne ML*, et al.* Magnetic resonance imaging during intracavitary gynecologic brachytherapy. *Int J Radiat Oncol Biol Phys* 1992;23:169-174.
39. Barillot I, Reynaud-Bougnoux A. The use of MRI in planning radiotherapy for gynaecological tumours. *Cancer Imaging* 2006;6:100-106.
40. Potter R, Fidarova E, Kirisits C*, et al.* Image-guided adaptive brachytherapy for cervix carcinoma. *Clin Oncol (R Coll Radiol)* 2008;20:426-432.
41. Zwahlen D, Jezioranski J, Chan P*, et al.* Magnetic Resonance Imaging-Guided Intracavitary Brachytherapy for Cancer of the Cervix. *Int J Radiat Oncol Biol Phys* 2008.
42. Haie-Meder C, Potter R, Van Limbergen E*, et al.* Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol* 2005;74:235-245.
43. Potter R, Haie-Meder C, Limbergen EV*, et al.* Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006;78:67-77.
44. Potter R, Dimopoulos J, Georg P*, et al.* Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. *Radiother Oncol* 2007;83:148-155.
45. Dimopoulos JC, Kirisits C, Petric P*, et al.* The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: clinical feasibility and preliminary results. *Int J Radiat Oncol Biol Phys* 2006;66:83-90.
46. Chan P, Yeo I, Perkins G*, et al.* Dosimetric comparison of intensity-modulated, conformal, and four-field pelvic radiotherapy boost plans for gynecologic cancer: a retrospective planning study. *Radiat Oncol* 2006;1:13.

47. Williamson D, Jezioranski J, Beiki-Ardakani A*, et al.* Optimization of Pulsed Dose Rate Intra-uterine Brachytherapy for Cancer of the Cervix: A Comparison of Target Volume Doses. *Int J Radiat Oncol Biol Phys* 2008;72:S367-S368.
48. Godfrey L, Hanley J, Napoli J*, et al.* Robotically-assisted minimally invasive brachytherapy: Pre-clinical aspects. *Int J Radiat Oncol Biol Phys* 2009;75:S721 Abs 3199.
49. Muntener M, Patriciu A, Petrisor D*, et al.* Magnetic resonance imaging compatible robotic system for fully automated brachytherapy seed placement. *Urology* 2006;68:1313-1317.
50. World Health Organisation. Cancer. 2010. www.who.int/cancer